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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,164	11/26/2003	Stephan R. Targan	025663-001201US	8299

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
ROONEY, NORA MAUREEN	

ART UNIT	PAPER NUMBER
1644	

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07/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,164	TARGAN ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,26 and 29-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-26, 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/16/2007 & 4/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants amendment filed on 04/14/2008 is acknowledged.

2. Claims 25-26 and 29-36 are pending and currently under consideration as they read on a method of determining a risk of having or developing a clinical subtype of Crohn's disease characterized by fibrostenosis, internal perforating disease or the need for small bowel surgery in a subject having Crohn's disease, comprising determining the presence or absence of three markers in the subject, said three markers being IgA anti-I2 antibodies, anti-Saccharomyces cerevisiae antibodies (ASCA), and IgA anti-OmpC antibodies.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 25-26 and 29-31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Targan et al. (PTO-892, Reference U) in view of Vasiliauskas et al. (Reference 30, IDS filed on

11/03/2004) and Landers et al. (Reference 17, IDS filed on 11/03/2004) for the same reasons as set forth in the Office Action mailed on 11/13/2007.

Applicant's arguments submitted on 04/14/2008 have been fully considered, but are not found persuasive.

Applicants argue:

"A. Biomarkers
The current claims are drawn to diagnostic methods for determining a risk of having or developing a clinical subtype of Crohn's disease. In contrast, Targan et al. teach the use of I2 and OmpC in assessing the likelihood of achieving efficacy in subjects with Crohn's disease with antibiotic therapy. The currently claimed method is much different than the art cited by the Examiner. In the claimed methods, the magnitude of IgA anti-I2 antibodies, anti- Saccharomyces cerevisiae antibodies (ASCA), and IgA anti-OmpC antibodies are measured and the risk of a subject is stratified using the foregoing measurements. The efficacy of antibiotic treatment as taught by Targan et al. has nothing at all to do with the claimed methods. Vasiliauskas et al. teach the use of ASCA and ANCA in stratifying Crohn's disease in patients. There is certainly no mention of IgA anti-I2 antibodies or IgA anti-OmpC antibodies and their use in assessing risk of various subtypes. Landers et al. aim was to assess the response to various antigens in Crohn's patients and the results showed that eighty-five percent responded to at least 1 antigen; and only 4% responded to all 4, whereas with microbial antigens, 78% responded to at least 1, 57% were double positive, but only 26% responded to all 3 (Abstract). The currently claimed methods for determining a risk of having or developing a clinical subtype of Crohn's disease are not taught or suggested.

B. Algorithm
In addition to the foregoing differences with respect to biomarkers, the currently claimed method recites unique method steps or an "algorithm," not taught or suggested by the cited art. The methods recite: a high magnitude of the three markers indicates a first risk; a high magnitude of exactly two of the three markers indicates a second risk; a high magnitude of exactly one of the three markers indicates a third risk; and the absence of a high magnitude of the three markers indicates a fourth risk. The unique "algorithm" is not obvious in view of the cited art.

In assessing the differences between the cited art and the claims at issue it is apparent that the references do not teach or suggest all the claim limitations. Moreover, at the time of the invention, an ordinary skilled artisan would not have found the differences in the claimed invention obvious. Applicants assert that the cited art does not teach or suggest all the claim limitations and therefore, *aprimafacie* case of obviousness simply has not been established. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection."

It remains the Examiner's position that Targan, et al., in view of Vasiliauskas, et al. and Landers, et al. does make the instant claims obvious, contrary to Applicant's assertion. Targan et al. describes a sub-type of Crohn's disease patients: those patients whose Crohn's disease is associated with antibodies to bacteria (OmpC and I2 antibodies) who would benefit from antibiotics to kill those bacteria. Whether the Targan, et al. reference conclusively determines a correlation between seroreactivity and the likelihood of success for a particular antibiotic therapy is not persuasive. Targan et al. is being relied on simply for it's teaching that a subset of Crohn's disease patients has the serological markers I2 and OmpC. Applicant's argument that unlike the cited reference, the present invention describes these markers in relation to their associations with specific Crohn's Disease subgroups, such as fibrostenosis is not persuasive. Vasiliauskas et al. teaches detecting ASCA and ANCA antibodies as a tool to stratify Crohn's disease into immunologically homogenous subgroups with distinct characteristic including fibrostenosis, internal perforating disease and the need for small bowel surgery. It would be obvious to one of ordinary skill in the art at the time of invention to further combine the OmpC and I2 markers to further stratify the fibrostenotic subgroups, especially given the fact that some types of Crohn's disease are associated with other bacterial markers as taught by Targan et al. and Landers et al. Further, Landers et al. and Vasilauskas et al. both teach using statistical analysis including Quartile analysis in particular as taught by Landers et al. to stratify patients based upon their serological marker phenotypes. One of ordinary skill in the art could arrive at the claimed invention given the reasoning set forth by the Examiner in the Office Action mailed on 01/29/2007. The Examiner only needs to set forth a logical reason to combine the references.

The reason to combine references need not be explicitly taught in the prior art, nor does the argument need to be for the same reasons that the Applicant used to invent.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 25-26 and 29-36 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons as set forth in the Office Action mailed on 07/25/2007. This is a New Matter rejection.

Applicant's arguments submitted on 04/14/2007 have been fully considered, but are not found persuasive.

> "The Examiner has rejected claims 25-26 and 29-36 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In response, Applicants respectfully traverse the rejection.

The Examiner alleges that the claims recite limitations that were not clearly disclosed in the specification and recited in the claims as originally filed in the priority application. Applicants respectfully traverse the rejection.

Applicants recite a method of obtaining a sample from the subject, and determining the level of three markers in the subj ect, i.e., IgA anti-I2 antibodies, anti- *Saccharomyces cerevisiae* antibodies (ASCA), and IgA anti-OmpC antibodies. This embodiment is clearly recited on page 28, lines 1-9, of U.S. Application No. 10/413,501, ("the 501 application") filed April 11, 2003, wherein it states:

A method of the invention for diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease in a subject having Crohn's disease by determining the presence or absence of IgA anti-I2 antibodies in the subject can *optionally* include the additional step of determining the presence or absence in the subject of a NOD2 variant, anti-Saccharomyces cerevisiae antibodies, IgA anti-OmpC antibodies, or perinuclear anti- neutrophil cytoplasmic antibodies (pANCA).

n the embodiment as currently claimed, anti-I2, anti-ASCA and anti-OmpC are determined, and therefore included, whereas NOD2 and anti-pANCA remain optional.

Further support for the claimed embodiments is found, for example, at page 6, lines 1-25 of the '501, wherein it states:

As disclosed herein, IgA antibodies to I2 were present in 56.5% of the Crohn's disease patients in the study (see Example I). Patients expressing IgA anti-I2 antibodies were significantly more likely to have a fibrostenotic subtype of Crohn's disease than those not expressing IgA anti-I2 antibodies (71.4% vs. 43.3%, p0.001) and significantly more likely to require small bowel surgery (66.7% vs. 37.1%, p0.001). In addition, IgA anti-I2 antibody expression was negatively associated with ulcerative colitis-like Crohn's disease (20.6% vs. 41.24%, p0.001). Quartile analyses revealed that higher levels of IgA anti-I2 antibodies were more strongly associated with the fibrostenotic subtype of Crohn's disease (p for the trend0.001) and small bowel involvement (p-0.023), and inversely associated with ulcerative colitis-like Crohn's disease (p=0.005) compared to lower levels of IgA anti-I2 antibodies. In addition, as disclosed in Example I, conditional analysis performed on NOD2 variants and ASCA indicated that IgA anti-I2 antibodies were independently associated with the fibrostenotic subtype (p=0.001 and p--0.005, respectively). Similarly, IgA anti-I2 was independently associated with small bowel surgery when conditioned on NOD2 variation (p=0.001) or ASCA (p=0.002). These results indicate that the presence of IgA anti-I2 antibodies can be used to diagnose or predict susceptibility to a clinical subtype of Crohn's disease, such as the fibrostenotic subtype, in a subject having Crohn's disease.

As further disclosed in Example I, patients with all three markers, IgA anti-I2 antibodies, one of the three NOD2 variants, and ASCA showed the greatest risk of the fibrostenotic subtype of Crohn's disease (82%, odds ratio=9.7, p0.000001), compared with patients with two markers (74%, odds ratio=6.0), one marker (48%, odds ratio=I.9), or none of these markers (33%, odds ratio=reference group). These results indicate that the presence of IgA anti-I2 antibodies in combination with the presence of other markers can be used to diagnose or predict susceptibility to a fibrostenotic subtype Crohn's disease in a patient having Crohn's disease.

The foregoing disclosure clearly shows that the greatest risk occurs with three markers, compared to two markers or with one marker. Quartile analysis was also performed and supports dependent claims.

Moreover, Applicants had clear support for OmpC antibodies as disclosed in the '501 application at the bottom of page 48, lines 25-30, bridging to page 49 at the top:

IgA anti-OmpC antibodies are another marker useful for determining a clinical subtype of Crohn's disease in a method of the invention. *IgA anti- OmpC antibodies are associated with the fibrostenotie subtype, need for small bowel surgery, and internal perforating disease subtype, and can be*

independently associated with the internal perforating disease subtype. Provided herein is a method of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease in a subject having Crohn's disease by determining the presence or absence of IgA anti-OmpC antibodies in the subject, where the presence of IgA anti-OmpC antibodies indicates that the subject has a clinical subtype of Crohn's disease. In one embodiment, the clinical subtype of Crohn's disease is the fibrostenotic subtype. In another embodiment, the clinical subtype of Crohn's disease is the internal perforating disease subtype.

The presence of IgA anti-OmpC antibodies in a subject can indicate that the subject has a fibrostenotic subtype of Crohn's disease. ***In some cases, the presence of IgA anti-OmpC antibodies can correlate with the*** *presence of ASCA. In some embodiments, the presence of IgA* ***anti- OmpC antibodies and ASCA are determined, while in other embodiments the presence of IgA anti-OmpC antibodies can be used as a surrogate marker for*** *thepresence ofASCA.* [Emphasis added].

Applicants had clear disclosure in the '501 application that in certain instances, *IgA anti-OmpC antibodies correlate with ASCA.* As is shown in Table 6 of the *current specification,* there is an increased likelihood of developing Crohn's disease characterized by fibrostenosing, internal perforating and small bowel surgery when an individual has immune reactivity to With regard to the *magnitude and number* of markers further support is found, for example, on page 16, lines 19-31, bridging to page 17 at the top of the '501 application, wherein it states:

The requirement for small bowel surgery in a subject with the fibrostenotic subtype of Crohn's disease can indicate a more aggressive form of this subtype. As shown in Example I, patients expressing IgA anti- I2 antibodies were significantly more likely to have the fibrostenotic subtype of Crohn's disease and significantly more likely to require small bowel surgery than those not expressing IgA anti-I2 antibodies. In addition, **the amplitude or level of Igh anti-I2 antibodies in a subject can be correlated with the likelihood of having a particular clinical sub,type of Crohn's disease. As shown in Example I~ quartile analyses revealed that higher levels of IgA anti-I2 antibodies were more strongly associated with the fibrostenotic subtype of Crohn's disease and small bowel involvement and were negatively associated with** exactly "1," "2," or "3" markers. **ulcerative colitis-like Crohn's disease than were lower levels. Furthermore~ the greater the number of fibrostenotic markers that a subject possesses~ the greater chance that the subiect will have an aggressive form of the fibrostenotic subtype of Crohn's disease requiring small bowel surgery (see Example I). For example~ a subject with two or more markers can have a more severe form of the fibrostenotic subtype than a patient with one marker.**

The foregoing support from the '501 application conveys with *reasonable clarity* to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention as now claimed. As the Examiner is well aware, and in accordance with MPEP § 2163.02, the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba)* in order for the disclosure to satisfy the description requirement. It is clear that Applicants were in possession of the invention as now claimed. 35 U.S.C. § 112, first paragraph requires no more. As such, Applicants respectfully request that the Examiner withdraw the rejection and send this application to issue.

It is the Examiner's position that Applicant has not provided clear support for the limitations at issue in the priority document, Application 10/413,501. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed in the 10/413,501 application priority document. Obviousness is not the

standard for the addition of new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977). New Matter is a written description issue. Applicant is creating a new method species. A subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads, see Inre Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571)

272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 3, 2008

Nora M. Rooney, M.S., J.D.

Patent Examiner

Technology Center 1600

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644